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ORIGINAL RESEARCH

Synthesis and cytostatic evaluation of some 2-(5-substituted-2-oxoindolin-3-ylidene)-*N*-substituted hydrazine carbothioamide

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Abstract Various substituted 2-(5-substituted-2-oxoindolin-3-ylidene)-*N*-substituted hydrazine carbothioamide **4a–g** and 2-(5-substituted-1-(4-substituted benzyl)-2-oxoindolin-3-ylidene)-*N*-substituted hydrazine carbothioamide **5a–k** were synthesized. The compounds were evaluated for their cytostatic activity against human Molt4/C8 and CEM T-lymphocytes as well as murine L1210 leukemia cells. Several of these compounds were endowed with low micromolar 50%-inhibitory concentration (IC_{50}) values, and some were virtually equally potent as melphalan. The most potent inhibitors against the murine leukemia cells were also most inhibitory against human T-lymphocyte tumor cells. 2-(5-fluoro-1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene)-*N*-*p*-tolylhydrazine carbothioamide (**5b**) emerged as the most potent cytostatic compound among the tested compounds. The encouraging cytostatic data provide an adequate rationale for further modification of these molecular scaffolds.

Keywords 2,3-dioxo-2,3-dihydroindole · Thiosemicarbazones · Cytostatic assays

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Introduction

Isatin has been known for about 150 years and has recently been found, like 2,3-dioxo-indoles and endogenous polyfunctional heterocyclic compounds, to exhibit biological activity in mammals (Somogyi, 2001). Isatin is also a synthetically versatile substrate that can be used to prepare a large variety of heterocyclic compounds, such as indoles and quinolines, and as a raw material for drug synthesis (Silva *et al*., 2001). Schiff bases and Mannich bases of isatin are known to possess a wide range of pharmacological properties including antibacterial (Pandeya *et al*., 1998; Sarangapani and Reddy, 1994; Varma and Nobles, 1975), anticonvulsant (Sridhar *et al*., 2002; Varma *et al*., 2004), anti-HIV (Pandeya *et al*., 1998 1999a, b 2000; Sriram *et al*., 2000), antifungal (Pandeya *et al*., 1999a, b), antiviral (Singh *et al*., 1983), and anticancer activity (Karki *et al*., 2004, 2007, 2009).

Thiosemicarbazones of various aldehydes and ketones occupy a special place among organic ligands, since they contain various donor atoms and are able to change density depending on the starting reagents and their reaction conditions. Isatin-3-thiosemicarbazones (1H-indole-2,3-dioxo-3-thiosemicarbazones) have been studied extensively due to their important biological activities (Karki *et al*., 2009), since 1-methylisatin-3-thiosemicarbazone (Marboran) was found to be active in the treatment of smallpox. Previous studies by our group have revealed the promising cytotoxic properties of various 2,3-dioxo-2,3-dihydroindole thiosemicarbazones (Karki *et al*., 2009). Therefore, we have performed the synthesis of new *N*-4-aryl thiosemicarbazone derivatives of substituted 2,3-dioxo-2,3-dihydroindoles and studied their antiproliferative activity against human Molt 4/C8 and CEM T-lymphocytes as well as murine L1210 leukemia cells.

Experimental

Chemistry

All reagents were obtained from Sigma-Aldrich Mumbai, and Loba Chemie, Mumbai. All the solvents used in these studies were dried and distilled before use. Melting points were recorded on a Veego VMP-PM digital melting point apparatus, and are uncorrected. FT-IR spectras were recorded on Shimadzu 8400 S, FT-IR. ^{1}H NMR spectra were recorded on 300 MHz JEOL NMR Spectrophotometer in $CDCl_3$ and DMSO-d_6. All spectras were obtained from Pune University, Maharashtra, India.

Synthesis of the intermediate indoline-2,3-diones

The synthesis of the intermediate indoline-2,3-diones was accomplished using a literature methodology (Marvel and Heirs, 1941), and a previously reported procedure was used to convert these compounds to the corresponding 1-benzylindoline-2,3-diones (Azizian *et al*., 2003). The *N*-4-arylthiosemicarbazides required in the preparation of **4a–g** and **5a–k** were prepared by a literature methodology (Sen and Sengupta, 1962; Lieber *et al*., 1957).

*General procedure for the synthesis of **4a–g** and **5a–k***

A mixture of the indoline-2,3-diones (**2**)/1-benzylindoline-2,3-dihydroindole (**3**) (0.005 mol), *N*-(4-substituted aryl)-thiosemicarbazides (0.005 mol), acetic acid (0.5–1.0 ml), and ethanol (100 ml) was heated under reflux until the reaction was completed (approximately 4 h). Approximately half of the ethanol was removed in vacuo, and the solution was left overnight at room temperature. The solid which precipitated was collected by filtration, washed with cold ethanol, and recrystallized from ethanol:chloroform (9:1) to give compounds **4a–g** and **5a–k**, respectively.

*2-(5-chloro-2-oxoindolin-3-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (**4a**)*

Yield 69%. mp 260–261°C. FT-IR ν_{max} cm^{-1} (KBr): 1129, 1289, 1686, 3061, 3143, 3226, 3246. ^{1}H-NMR δ: 6.9–7.8 (m, 7H, Ar–H), 10.94 (s, 1H, CO–NH), 11.38 (s, 1H, N–NH), 12.66 (s, 1H, NH).

*2-(5-bromo-2-oxoindolin-3-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (**4b**)*

Yield 86%. mp 255–258°C. FT-IR ν_{max} cm^{-1} (KBr): 1131, 1295, 1672, 3019, 3113, 3220, 3250 ^{1}H-NMR δ: 6.9–8.0 (m, 7H, Ar–H), 10.94 (s, 1H, CO–NH), 11.38 (s, 1H, N–NH), 12.66 (s, 1H, NH).

*2-(5-bromo-2-oxoindolin-3-ylidene)-N-p-tolylhydrazine carbothioamide (**4c**)*

Yield 76%. mp 255–260°C. FT-IR ν_{max} cm^{-1} (KBr): 1184, 1315, 1692, 3015, 3123, 3212, 3248. ^{1}H-NMR δ: 2.51 (s, 3H, CH_3), 6.9–8.0 (m, 7H, Ar–H), 10.86 (s, 1H, CO–NH), 11.36 (s, 1H, N–NH), 12.59 (s, 1H, NH).

*2-(5-fluoro-2-oxoindolin-3-ylidene)-N-p-tolylhydrazine carbothioamide (**4d**)*

Yield 78%. mp 276–280°C. FT-IR ν_{max} cm^{-1} (KBr): 1154, 1291, 1682, 2995, 3116, 3234, 3256. ^{1}H-NMR δ: 2.51 (s, 3H, CH_3), 6.9–7.6 (m, 7H, Ar–H), 10.81 (s, 1H, CO–NH), 11.27 (s, 1H, N–NH), 12.65 (s, 1H, NH).

*2-(6-chloro-5-fluoro-2-oxoindolin-3-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (**4e**)*

Yield 70%. mp 278–280°C. FT-IR ν_{max} cm^{-1} (KBr): 1164, 1317, 1698, 3019, 3133, 3213, 3243. ^{1}H-NMR δ: 6.9–7.8 (m, 6H, Ar–H), 10.2 (s, 1H, CO–NH), 11.54 (s, 1H, N–NH), 12.63 (s, 1H, NH).

*2-(6-chloro-5-fluoro-2-oxoindolin-3-ylidene)-N-p-tolylhydrazine carbothioamide (**4f**)*

Yield 69%. mp 267–270°C. FT-IR ν_{max} cm^{-1} (KBr): 1180, 1310, 1672, 3010, 3128, 3215, 3237. ^{1}H-NMR δ: 3.27 (s, 3H, CH_3), 6.9–7.8 (m, 6H, Ar–H), 10.14 (s, 1H, CO–NH), 11.52 (s, 1H, N–NH), 12.62 (s, 1H, NH).

*N-(4-chlorophenyl)-2-(5-fluoro-2-oxoindolin-3-ylidene)hydrazine carbothioamide (**4g**)*

Yield 73%. mp 290–293°C. FT-IR ν_{max} cm^{-1} (KBr): 1165, 1295, 1682, 3008, 3121, 3210, 3238. ^{1}H-NMR δ: 6.6–7.8 (m, 7H, Ar–H), 11.10 (s, 1H, CO–NH), 11.29 (s, 1H, N–NH), 12.52 (s, 1H, NH).

*N-(4-chlorophenyl)-2-(5-fluoro-1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene)hydrazine carbothioamide (**5a**)*

Yield 74%. mp 197–200°C. FT-IR ν_{max} cm^{-1} (KBr): 1119, 1298, 1696, 3042, 3129, 3214, 3257. ^{1}H-NMR δ: 5.0 (s, 2H, CH_2), 7.0–7.7 (m, 11H, Ar–H), 10.96 (s, 1H, N–NH), 12.65 (s, 1H, NH).

*2-(5-fluoro-1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene)-N-p-tolylhydrazine carbothioamide (**5b**)*

Yield 77%. mp 230–235°C. FT-IR ν_{max} cm^{-1} (KBr): 1126, 1287, 1681, 3054, 3143, 3212, 3251. ^{1}H-NMR δ: 2.35 (s,

3H, CH_3), 5.0 (s, 2H, CH_2), 7.0–7.8 (m, 11H, Ar–H), 10.87 (s, 1H, N–NH), 12.58 (s, 1H, NH).

*2-(5-chloro-1-(4-methylbenzyl)-2-oxoindolin-3-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (**5c**)*

Yield 86%. mp 235–239°C. FT-IR ν_{max} cm^{-1} (KBr): 1135, 1294, 1682, 3026, 3119, 3243, 3264. ^{1}H-NMR δ: 2.51 (s, 3H, CH_3), 5.01 (s, 2H, CH_2), 7.0–8.7 (m, 11H, Ar–H), 11.00 (s, 1H, N–NH), 12.58 (s, 1H, NH).

*2-(5-chloro-1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (**5d**)*

Yield 66%. mp 238–240°C. FT-IR ν_{max} cm^{-1} (KBr): 1126, 1310, 1706, 3047, 3127, 3237, 3276. ^{1}H-NMR δ: 4.96 (s, 2H, CH_2), 7.0–7.9 (m, 11H, Ar–H), 10.99 (s, 1H, N–NH), 12.61 (s, 1H, NH).

*2-(5-chloro-1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (**5e**)*

Yield 81%. mp 230–235°C. FT-IR ν_{max} cm^{-1} (KBr): 1156, 1295, 1696, 3056, 3123, 3219, 3259. ^{1}H-NMR δ: 5.00 (s, 2H, CH_2), 7.0–7.9 (m, 11H, Ar–H), 10.99 (s, 1H, N–NH), 12.59 (s, 1H, NH).

*2-(5-bromo-1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (**5f**)*

Yield 73%. mp 240–245°C. FT-IR ν_{max} cm^{-1} (KBr): 1134, 1287, 1685, 3014, 3161, 3206, 3245. ^{1}H-NMR δ: 5.0 (s, 2H, CH_2), 7.0–8.0 (m, 11H, Ar–H), 11.0 (s, 1H, N–NH), 12.59 (s, 1H, NH).

*2-(5-bromo-1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene)-N-p-tolylhydrazine carbothioamide (**5g**)*

Yield 80%. mp 268–270°C. FT-IR ν_{max} cm^{-1} (KBr): 1125, 1309, 1694, 3081, 3123, 3204, 3261. ^{1}H-NMR δ: 2.37 (s, 3H, CH_3), 4.95 (s, 2H, CH_2), 6.9–8.0 (m, 11H, Ar–H), 10.92 (s, 1H, N–NH), 12.52 (s, 1H, NH).

*2-(5-bromo-1-(4-methylbenzyl)-2-oxoindolin-3-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (**5h**)*

Yield 81%. mp 220–223°C. FT-IR ν_{max} cm^{-1} (KBr): 1124, 1295, 1710, 3004, 3153, 3210, 3251. ^{1}H-NMR δ: 2.27 (s, 3H, CH_3), 4.96 (s, 2H, CH_2), 7.0–8.0 (m, 11H, Ar–H), 11.00 (s, 1H, N–NH), 12.61 (s, 1H, NH).

*2-(5-bromo-1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene)-N-p-tolylhydrazine carbothioamide (**5i**)*

Yield 72%. mp 217–220°C. FT-IR ν_{max} cm^{-1} (KBr): 1094, 1269, 1686, 3043, 3113, 3206, 3243. ^{1}H-NMR δ: 2.51 (s, 3H, CH_3), 3.35 (s, 2H, CH_2), 7.0–8.0 (m, 11H, Ar–H), 10.92 (s, 1H, N–NH), 12.51 (s, 1H, NH).

*2-(5-bromo-1-(4-methylbenzyl)-2-oxoindolin-3-ylidene)-N-p-tolylhydrazine carbothioamide (**5j**)*

Yield 79%. mp 185–190°C. FT-IR ν_{max} cm^{-1} (KBr): 1126, 1309, 1698, 3056, 3133, 3218, 3239. ^{1}H-NMR δ: 2.27 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.96 (s, 2H, CH_2), 6.9–8.0 (m, 11H, Ar–H), 10.92 (s, 1H, N–NH), 12.54 (s, 1H, NH).

*2-(5-bromo-1-(4-chlorobenzyl)-2-oxoindolin-3-ylidene)-N-(4-chlorophenyl)hydrazine carbothioamide (**5k**)*

Yield 76%. mp 230–233°C. FT-IR ν_{max} cm^{-1} (KBr): 1120, 1296, 1684, 3046, 3135, 3216, 3247. ^{1}H-NMR δ: 4.94 (s, 2H, CH_2), 6.4–7.7 (m, 11H, Ar–H), 11.29 (s, 1H, N–NH), 12.52 (s, 1H, NH).

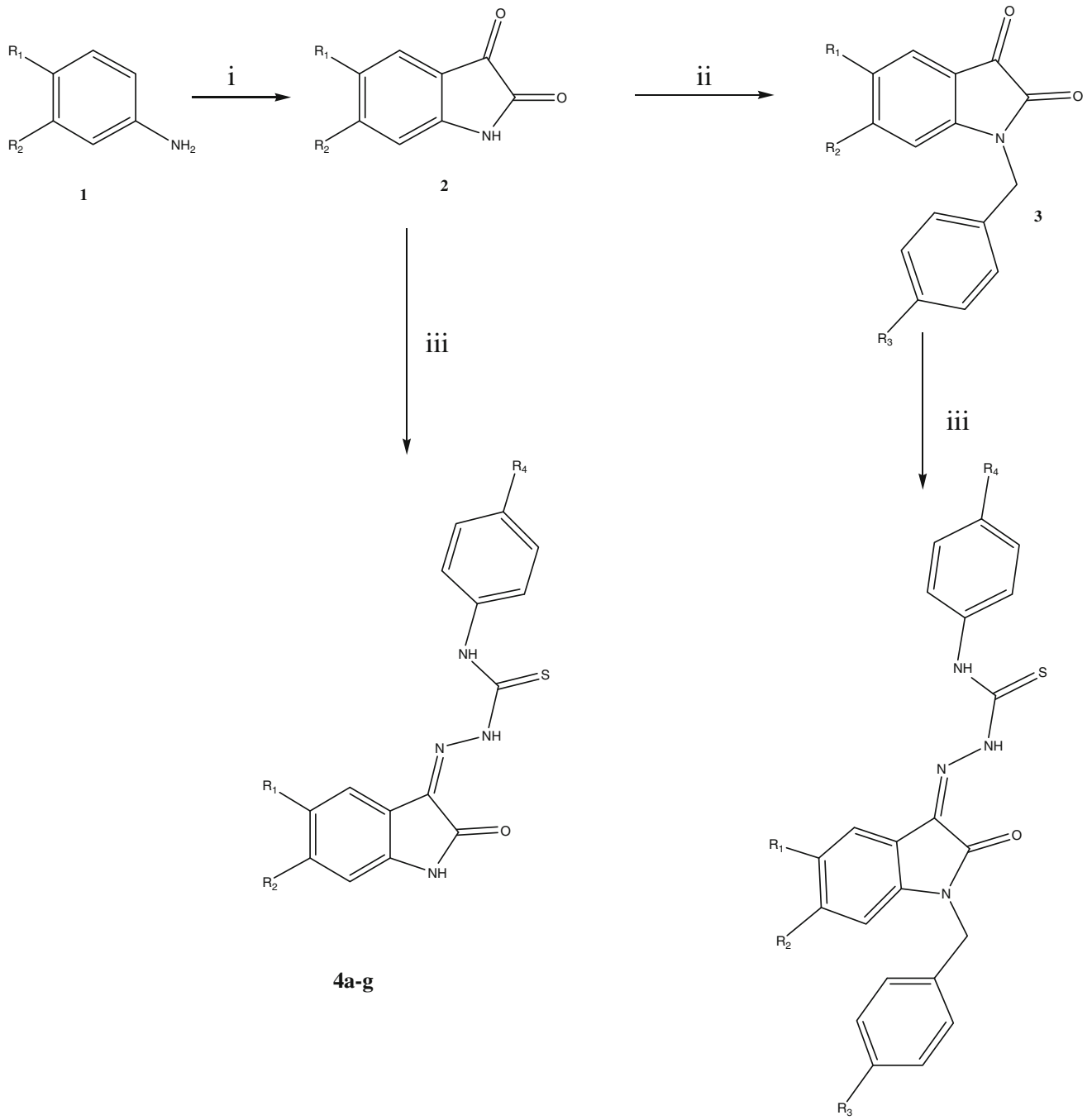
Cytostatic assays

The methodology for undertaking the antiproliferative assays has been published previously (Baraldi *et al*., 2004). In brief, varying concentrations of the compounds (5-fold dilutions) were incubated at 37°C for 72 h (Molt4/C8 and CEM T-lymphocytes) or 48 h (L1210 cells) in 200 µl 96-well microtiter plates, and the viable tumor cell number was counted at the end of the incubation period using a Coulter Counter (Coulter Electronics, Harpenden Hertz, U.K.).

Results and discussion

Chemistry

The compounds in series **4** and **5** were prepared by the methodologies outlined in Scheme 1. The synthesis of *N*-benzyl-2,3-dioxoindole (**3**) was carried out by reacting benzyl chloride with various 2,3-dioxo-indoles in the presence of potassium carbonate under reflux in DMF. The synthesis of the 2,3-dioxo-2,3-dihydroindolo-thiosemicarbazones (**4a–g, 5a–k**) was carried out by the condensation of various 2,3-dioxoindoles/*N*-arylalkyl-2,3-dioxoindoles (2,3) with aryl thiosemicarbazide under reflux in ethanol in the presence of catalytic amounts of glacial acetic acid. ^{1}H NMR spectroscopy indicated that the compounds exist as



Scheme 1 Synthesis of compounds **4a–g and 5a–k**. The reagents used are as follows: *i* $CCl_3CH(OH)_2/H_2SO_4/Na_2SO_4$; *ii* R_3-$C_6H_4CH_2Cl/K_2CO_3$/DMF; *iii* R_4-$C_6H_4NHCSNHNH_2$. The nature of the R_1, R_2, R_3, and R_4 substituents are presented in Table 1

single isomers in solution. The compounds adopted the *Z* conformation (Karki *et al*., 2009).

Biological activity

The compounds were evaluated for their cytostatic activity against human Molt4/C8 and CEM T-lymphocytes as well as murine L1210 leukemia cells. The data are summarized in Table 1.

Several compounds (**4c–d and 5b–c**) showed IC_{50} values in the low micromolar range (1–10 μM). Molt4/C8 cells were slightly more sensitive to the cytostatic activity of the compounds in both series **4** and **5** than CEM or L1210 cells.

Table 1 Cytostatic activity of test compounds against murine L1210 leukemia and human Molt4/C8 and CEM T-lymphocyte cells

Comp. code	Substituents				IC_{50}* (μM)		
	R_1	R_2	R_3	R_4	L1210	Molt4/C8	CEM
4a	Cl	H	H	Cl	108 ± 18	64 ± 20	61 ± 6
4b	Br	H	H	Cl	88 ± 39	29 ± 16	61 ± 11
4c	Br	H	H	CH_3	9.6 ± 1.8	4.9 ± 3.5	6.8 ± 2.4
4d	F	H	H	CH_3	8.2 ± 3.6	3.0 ± 0.7	4.8 ± 0.5
4e	F	Cl	H	Cl	69 ± 50	43 ± 10	48 ± 18
4f	F	Cl	H	CH_3	166 ± 48	112 ± 81	132 ± 75
4g	F	H	H	Cl	34 ± 2	14 ± 7	25 ± 6
5a	F	H	F	Cl	154 ± 73	47 ± 3	56 ± 14
5b	F	H	F	CH_3	6.2 ± 2.1	1.5 ± 1.1	2.5 ± 1.2
5c	Cl	H	CH_3	Cl	9.8 ± 2.1	5.8 ± 4.2	18 ± 9
5d	Cl	H	Cl	Cl	124 ± 39	58 ± 13	68 ± 1
5e	Cl	H	F	Cl	103 ± 53	48 ± 5	50 ± 14
5f	Br	H	F	Cl	196 ± 66	48 ± 7	61 ± 9
5g	Br	H	F	CH_3	190 ± 40	57 ± 9	132 ± 35
5h	Br	H	CH_3	Cl	193 ± 49	74 ± 19	98 ± 14
5i	Br	H	Cl	CH_3	≥ 500	288 ± 12	≥500
5j	Br	H	CH_3	CH_3	>500	393 ± 27	≥500
5k	Br	H	Cl	Cl	≥500	280 ± 43	392 ± 104
Melphalan	–	–	–	–	2.1 ± 0.02	3.2 ± 0.6	2.5 ± 0.2

* The IC_{50} values represent the compound concentrations required to inhibit the growth of the tumor cells by 50%

There was, in general, a strong correlation between the three tumor cell lines regarding the cytostatic activities of the compounds. The most potent inhibitors of murine L1210 cell proliferation (i.e., **4c** and **4d**, and **5b** and **5c**) were also most inhibitory to human T-lymphocyte CEM and Molt4/C8 cell proliferation. Also, the scaffold of the most potent cytostatic compound in the **4** series (**4d**) was most inhibitory in the **5** series (**5b**). In the majority of cases, introduction of the R_3-benzyl substituent in the thiosemicarbazone derivative series **5** often led to (slightly) less potent inhibitors of tumor cell proliferation. In a number of cases, replacement of the chloro at R_4 by a methyl resulted in a marked potentiation of the cytostatic activity (compare 4**b** with **4c**; **4g** with **4d**; **5a** with **5b**) (Table 1). In the **5** series of compounds, replacement of the chlorine atom at R_1 by a bromine often resulted in a decreased activity; i.e., compare **5c** with **5h**; **5d** with **5k**; and **5e** with **5f.**

Conclusion

Two series of derivatives of 2,3-dioxo-2,3-dihydroindol-(*N*-4-substituted aryl)-thiosemicarbazones were prepared in good yields. All compounds were evaluated for cytostatic activity against human Molt4/C8 and CEM T-lymphocytes and murine L1210 leukemia cells. The compounds **4c**, **4d**, **5b**, and **5c** had IC_{50} values in the low micromolar range (1–10 μM). Among the tested compounds, **5b** and **4d** had antiproliferative potencies that were close to those obtained for melphalan and should be the basis for further synthesis of more potent cytostatic agents.

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